



Adenovirus Vaccine Restoration

**Presentation to
Armed Forces Epidemiological Board**

Dr. Lawrence Lightner
Project Manager for Pharmaceutical Systems
U.S. Army Medical Research & Materiel Command

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Outline

- Program Status Overview
- Phase 1 Clinical Study
- Vaccine Manufacturing
- Regulatory
- Near Term Plan/Events
- Program Risks



Objective

Provide a safe, efficacious, FDA approved Adenovirus Vaccine (Type 4 and 7) to protect US military trainees from adenovirus disease.

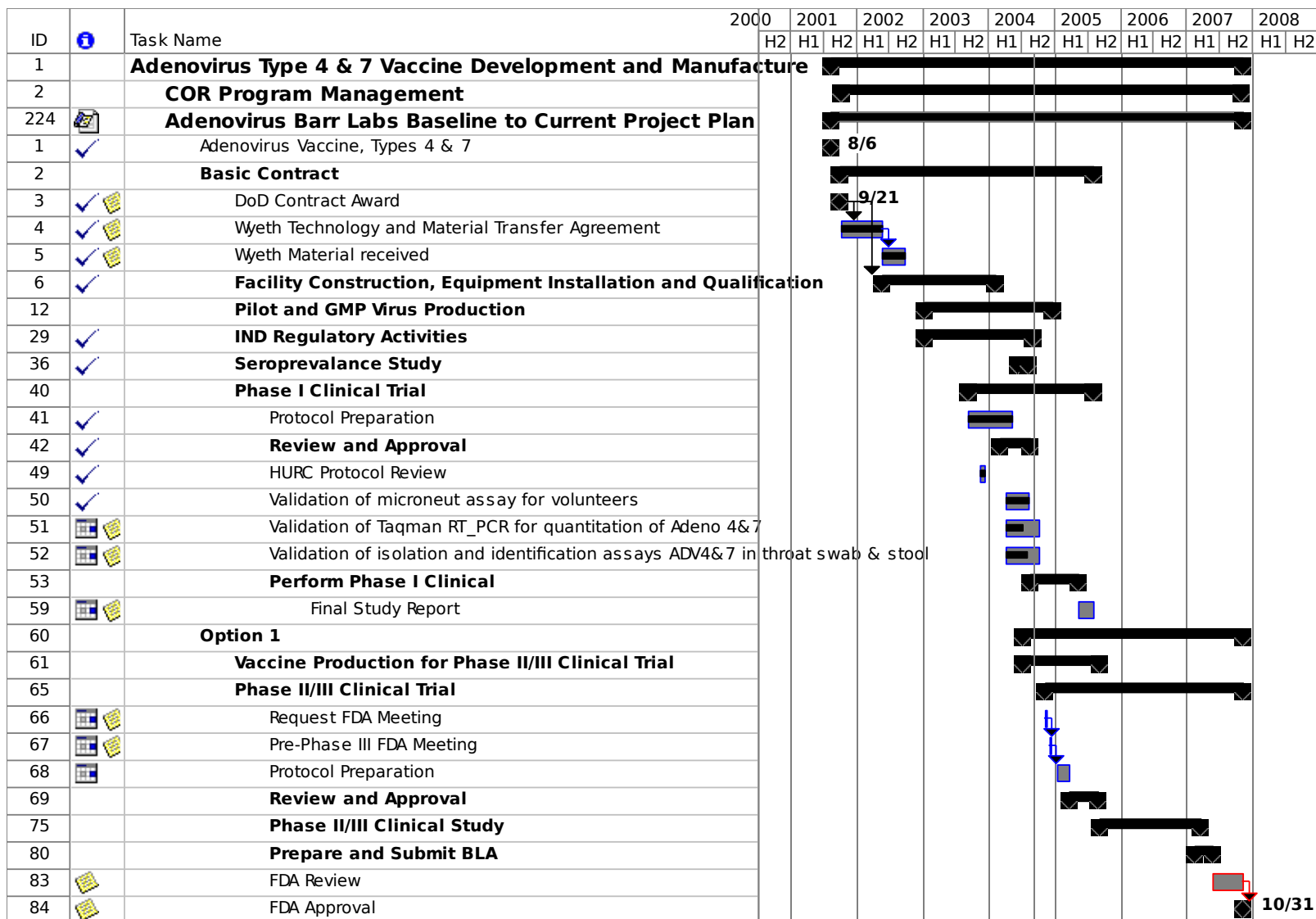


Defense Health Program Requirement

In consultation with the AFEB, ASD(HA) officially established a Defense Health Program requirement for adenovirus vaccine type 4 and type 7 to protect military recruits against adenovirus infection (Letter dated 3 February 2005)



Development Plan-Sep04





Development Plan-Mar05



ID	Task Name	Start	Finish	2001	2002	2003	2004	2005	2006	2007	2008	2009
				H1	H2	H1	H2	H1	H2	H1	H2	H1
1	Adenovirus Vaccine, Types 4 & 7	Mon 8/6/01	Mon 8/6/01		8/6							
2	Basic Contract	Mon 8/6/01	Tue 8/23/05									
3	DoD Contract Award	Fri 9/21/01	Fri 9/21/01		9/21							
4	Wyeth Technology and Material Transfer Agreement	Mon 10/1/01	Fri 5/17/02		10/1	5/17						
5	Wyeth Material received	Mon 5/20/02	Mon 9/16/02		5/20	9/16						
6	Facility Construction, Equipment Installation and Qualification	Fri 5/17/02	Fri 1/30/04									
12	Pilot and GMP Virus Production	Mon 1/6/03	Fri 2/25/05									
34	IND Regulatory Activities	Thu 1/9/03	Tue 8/24/04									
41	Seroprevalance Study	Wed 6/2/04	Fri 7/30/04									
45	Phase I Clinical Trial	Mon 8/6/01	Tue 8/23/05									
46	Protocol Preparation	Mon 9/1/03	Mon 5/3/04			9/1	5/3					
47	Review and Approval	Mon 8/6/01	Mon 8/9/04									
57	Assays and Data Analysis	Wed 3/31/04	Thu 3/31/05									
67	Execute Phase I Clinical Protocol	Fri 8/13/04	Wed 5/18/05									
92	Site Requirements	Tue 11/30/04	Tue 8/23/05									
96	Option 1	Wed 8/4/04	Thu 5/1/08									
97	Vaccine Production for Phase II/III Clinical Trial	Wed 8/4/04	Mon 7/3/06									
112	Bulk Virus Production and testing	Fri 10/1/04	Wed 6/8/05									
124	Lyophilization at WRAIR	Mon 2/21/05	Fri 4/29/05									
129	Lyophilization at VA	Wed 8/4/04	Fri 5/27/05									
135	Vaccine Tablet Production and testing in VA for Next C	Mon 3/28/05	Fri 8/19/05									
143	Long term stability testing for the phase III product	Mon 8/22/05	Fri 7/20/07					8/22		7/20		
144	Phase II/III Clinical Trial	Thu 12/2/04	Thu 5/1/08									
145	Develop Clinical Protocols	Thu 12/2/04	Thu 5/26/05									
173	Repro Tox Study	Fri 1/14/05	Tue 7/18/06									
176	Review and Approval	Fri 5/27/05	Fri 9/16/05									
183	Phase II/III Clinical Study	Fri 9/16/05	Wed 4/4/07									
201	QA Audits	Mon 9/5/05	Fri 1/19/07					9/5		1/19		
202	Write Reports	Wed 5/10/06	Fri 7/14/06									
205	Prepare and Submit BLA	Thu 2/22/07	Thu 5/31/07									
208	FDA Review	Fri 6/1/07	Thu 11/15/07							6/1	11/15	
209	FDA Approved	Thu 11/15/07	Thu 11/15/07								11/15	
210	Product Availability	Fri 11/16/07	Thu 5/1/08							11/16	5/1	



Funding Requirements

- ASD(HA) directed funding in FY04 and FY05 to cover cost increase in program
 - Scope change (re-development)
 - Indirect cost increase (DCAA audit)
- Funding is programmed to support the current contract cost estimate FY05-07
 - Cost plus fixed fee contract
- Program funds are required for initial procurement in FY08 and vaccine sustainment in out years



Sustainment

- Defense Supply Center, Philadelphia
 - Product Manager met with DSC,P managers to discuss logistics, management, and funding of licensed vaccine
- Barr Labs to provide updated vaccine cost estimate in May 2005



Clinical Development Status

A Phase 1, Randomized, Double-Blind, Placebo Controlled Study to Evaluate The Safety And Immunogenicity Of The Live, Oral Type-4 and Type-7 Adenovirus Vaccines is in progress



Phase 1 Study Objectives

Primary:

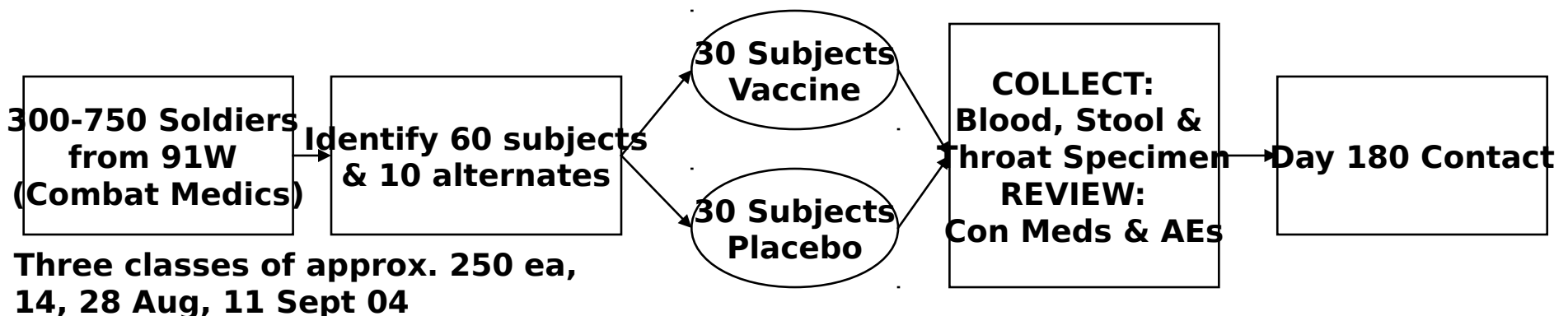
1. Evaluation of the safety of the type 4 and type 7 oral adenovirus vaccines administered together.

Secondary:

1. Evaluation of the immune response (neutralizing antibody titer and seroconversion rate) to the type 4 and the type 7 oral adenovirus vaccines.
2. Characterization of the duration of vaccine virus shedding in the stool and throat secretions in vaccine recipients.



Study Design



SCREENING
Day -28

RANDOMIZED
Day 0 Baseline
(25 SEP 04)

F/U visits on
Days 7, 14, 21,
28 & 56

Visit - Telephone
or Letter

FDA Requirement

Need Serology Report

Staff

5 Lab Tech
45 Clinical Research Nurse (CRN)
5-7 AD MDs
1 Officer, 2 NCO's
3 Barr Floaters

Staff

5 Lab Tech
5 CRN
3-5 AD MDs
1 Officer, 2 NCO's
1-3 Barr Floaters

Staff

PI
Lead CRN

1 1



Phase 1 Execution

- 412 volunteers screened (8/14 to 9/11/04)
- 58 volunteers enrolled (9/26/04)
 - Volunteers enrolled were seronegative for adenovirus type 4 or 7 or both when screened
- 58 volunteers vaccinated (9/26/04)
- 54 volunteers completed study (11/21/04)
 - 4 volunteers dropped out (not vaccine related)
- 180 day follow-up will be complete by 24Mar05

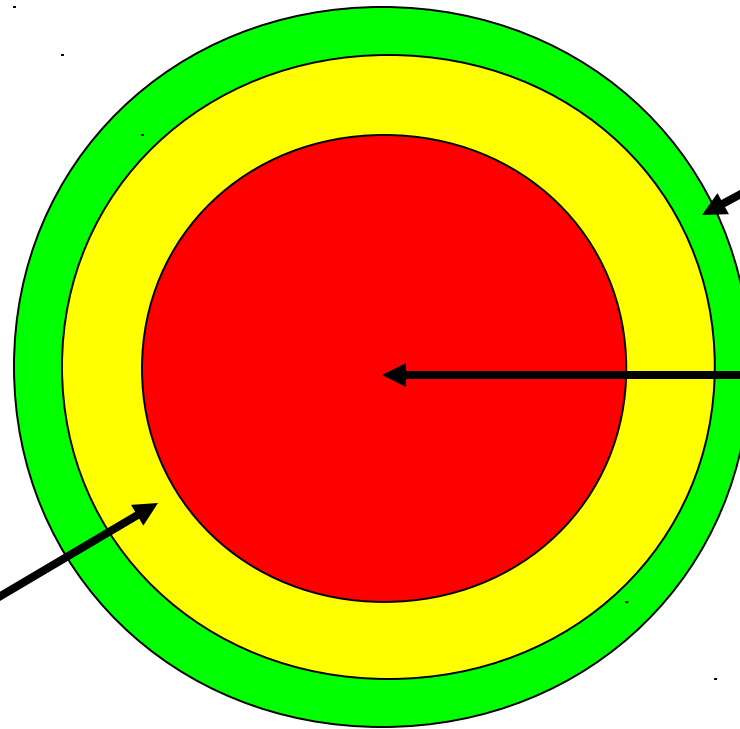


Phase 1 Execution

- Clinical sample testing began Nov04
- Testing is expected to be complete on 31Mar05
- Scheduled to unblind the study on 7Apr05
- Observations from the study to date...
 - The vaccine was well tolerated
 - Serconversion was observed
 - Virus shedding was observed
 - No training days were lost due to vaccine side-effects



Vaccine Manufacturing



Polymer Coating

Inner Virus Core

Outer Core Inert Material



Provided by Barr/VaccGen



Vaccine Manufacturing

- Current status of vaccine manufacturing
 - Stability of Phase 1 vaccines
 - Further formulation development of vaccines
 - Switch to MRC-5 cell substrate to improve virus production
- Potential impact of manufacturing changes
 - Unforeseen difficulties in scale-up and production
 - Delay in schedule due to shift in cell substrate
 - Cost increase



Regulatory

- Sponsor (Barr) requested a meeting with FDA (11March2005)
- FDA responded (16March2005) that the meeting request was somewhat premature
- FDA agreed to meet after unblinding of phase 1 trial results to:
 - discuss Phase 1 trial data
 - assist in planning next clinical trial
 - discuss CMC issues



Next Clinical Study

- Currently evaluating clinical trial sites
 - ASD(HA) requested all services basic training installations provide support for clinical trial
 - TRADOC has agreed to support testing at Ft Jackson and Ft Leonard Wood; the Navy will support testing at Great Lakes
 - Initial visits have been made to Ft. Jackson (9Mar05) and Great Lakes (23Mar05)
- Execution of the current clinical plan is dependent on:
 - The outcome of Phase 1 trial and meeting with the FDA
 - Vaccine manufacturing and availability of vaccine lots for testing
 - Integration with the Services' training schedule



Moving Forward

- **Next 3 months**

- Report on Phase 1 Clinical Trial (May 05)
- Plan for next clinical trial
 - Study design
 - Site selection
- Plan for FDA follow-up
 - Continue planning for next clinical trial
- Manufacturing
 - Additional vaccine stability testing
 - Complete validation of lyophilization equipment in tablet facility
- Produce additional bulk virus
 - MRC-5 derived (3 lots each type by end of Aug 2005)
 - WI-38 (Finished)
- Produce additional vaccine
 - MRC-5 derived (3 lots each type by Dec 2005)
 - WI-38 derived (1 lot each type by Sep 2005)



Moving Forward

- Next 6-9 months
 - Re-qualify manufacturing facility
 - Produce additional vaccine
 - Solidify plan for next clinical trial
 - Initiate clinical protocol at approved sites



Program Risks

- Vaccine Performance
 - Manufacturing
 - Effectiveness
- Production failures
- Regulatory (FDA) directions
- Integration of trials with basic training schedules

Any or all of the above could impact baseline performance, schedule, and cost